

REMARKS

Claim 8 has been amended to specifically recite SEQ ID NO:5, the polypeptide encoded by elected sequence, SEQ ID NO:10. Claim 10 has been amended to recite the phrase “completely complementary”. Support for the amendment to claim 10 is found in the specification, for example, at page 8, lines 20-22, which defines “complete” complementarity. No new matter is added by these amendments, and entry of the amendments is requested.

Election/Restriction

The Examiner stated that applicants election of Group II, corresponding to claims 3-6, 10 and 11 and further election of SEQ ID NO:10, with traverse, is acknowledged, however, that unity of invention does not exist between the inventions of Groups I-VI, specifically, because the only technical feature linking the groups appears to be that they all relate to the expression of leukocyte and blood-associated proteins. However, the Examiner stated, Leavitt et al., U.S. Patent No. 5,002,870 teach the expression of leukocyte and blood-associated proteins and the polynucleotides encoding them. Therefore, the technical feature linking the inventions of Groups I-VI does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.



The requirement is still deemed proper and made Final. Claims 1-2, 8-9, 12-16, 19 and 22-27 are withdrawn from further consideration.

Applicants Response

Applicants strongly disagree with the Examiner's assessment that the only technical feature linking applicants claims is the generic association of applicants invention to “leukocyte and blood associated proteins”. Applicants reiterate that, in accordance with PCT Rule 13.2, and the corresponding section of the MPEP, § 1893.03(d), the special technical feature linking Groups I-IV is the specific polynucleotide sequences of SEQ ID NOs:6-10 and their corresponding encoded polypeptides, SEQ ID NOs:1-5. See page 9 of Applicants Response to the Restriction Requirement, filed November 21, 2003. Leavitt et al do not teach the specific sequences of SEQ ID NOs:1-5 or SEQ ID NOs:6-10 which clearly define a contribution over the prior art. In particular, elected SEQ ID NO:10 encoding SEQ ID NO:5 are so defined. Applicants therefore reserve the right to petition the Examiners restriction in the course of prosecution of this application..

35 U.S.C. § 112, Second Paragraph, Rejection of Claims 10-11

The Examiner has rejected claims 10-11 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that in claim 10, the term “complementary to” allows for a multiplicity of interpretations. The term could mean a nucleotide sequence that has a high degree of homology to the original, that comprises the original, or that resembles the original in regards to structural integrity.

Applicants Response

Claim 10 has been amended to recite “completely complementary” as defined at page 8 of the specification. The claims, as amended are therefore clear and definite, and withdrawal of the rejection of claims 10-11 under 35 U.S.C. § 112, second paragraph is requested.

35 U.S.C. § 101, Rejection of Claims 3-6, 10 and 11

The Examiner has rejected claims 3-6, 10 and 11 under 35 U.S.C. § 101, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 3-6, 10 and 11 are directed to isolated nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO:10 that encode the protein comprising the amino acid sequence of SEQ ID NO:5. SEQ ID NO:5 is disclosed as a protein that shares structural and sequence similarity with leukocyte and blood associated proteins.

The instant application describes the uses and methods of the invention, and state that the nucleic acid molecules and proteins are useful in methods such as screening, detecting assays, production of expression vectors, manufacture of medicament for the treatment of a variety of diseases, production of antibodies for diagnostic purposes. The specification further states that the LBAP proteins (in particular, LBAP-5) have structural similarity with a putative haemopoietic membrane proteins (g3355655). The specification further asserts that the LBAP proteins of the invention can be used for screening for drugs effective in the treatment of the symptomatic or phenotypic manifestations of perturbing the normal function of the immune system of the body and can be used directly to treat diseases and disorders.

However, the Examiner stated, these are not considered to be specific or substantial utilities for either the nucleic acid molecules or proteins. The methods such as recombinant

protein production, detecting assays, antibody production, etc., are considered to be general methods, and are not considered specific and substantial utilities.

It is asserted in the specification that LBAP-5 encoded by SEQ ID NO:10 has structural similarity with putative haemopoietic membrane proteins (g3355655; Kalin et al. and Baird et al., cited in the IDS). However, LBAP-5 has not been shown to have primary structural similarity with g3355655. Also, the Examiner stated, there is no disease or disorder correlated with LBAP-5. Based on structural similarity alone, the specification attempts to assert that the new cDNA clone encoded a putative haemopoietic membrane protein. However, function prediction from structure or structure prediction from function is not a reliable measure of utility.

The Examiner suggested that the instant case is similar to that of *Brenner v. Manson* (Sup Ct. 1966) in which a novel compound that was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of direct evidence supporting this utility. The court held this broad interpretation that all chemical compounds are “useful” was not the intended definition of useful as it appears in 35 U.S.C. 101, which requires that an invention must have either an immediately obvious or fully disclosed “real world” utility. The instant claims are drawn to polynucleotides encoding novel proteins which have undetermined function or biological significance. Thus, the Examiner stated, no actual or specific activity is attributed to the proteins identified in the specification as novel human proteins or the polynucleotides encoding them.

Applicants Response

Applicants disagree that neither a specific and substantial asserted utility nor a well established utility is apparent to the skilled artisan from the specification and the knowledge of the skilled artisan at the time the application was filed.

Appellants' invention is directed to polynucleotides encoding a polypeptide sequence of SEQ ID NO:5, LABP-5. LABP-5 is characterized in the specification and the art of record as a putative haemopoietic membrane protein based on a high degree of sequence homology (77% identical) with a mouse haemopoietic membrane protein, JB 542 (g3355655). See specification, Table 2, and attached sequence alignment, Exhibit A. JB542 is characterized in the art of record as a novel protein expressed in primary, undifferentiated haemopoietic cells, whose expression drops markedly upon cellular differentiation. See Baird et al. (2001), IDS reference #1, pp.

9192-9193. JB542 is therefore identified as a potential cell surface marker in haemopoietic stem cell differentiation. LABP-5 is furthermore disclosed in the specification as found exclusively in a primary osteogenic sarcoma cell line derived from a human bone tissue library, BONEUNT01. See specification, at Tables 3 and 4. The claimed polynucleotide and its encoded protein are therefore asserted to be useful in the diagnosis and treatment of cell proliferative disorders, including autoimmune/inflammatory disorders and cancer, as well as markers for stem cell differentiation.

The rejection of claims 3-6, 10 and 11 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide corresponding to a gene that is expressed in osteogenic tissue. The novel polynucleotide codes for a polypeptide demonstrated in the patent specification to be a member of the class of haemopoietic proteins involved in stem cell differentiation. The claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. It is furthermore noted that the claimed polynucleotide and its encoded polypeptide are potentially useful markers for stem cell differentiation. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Applicants submit three expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references filed before the March 1, 1999 priority date of the instant application describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Rockett Declaration, Iyer Declaration, Bedilion Declaration, and the ten (10) references fully establish that, prior to the March 1, 1999 filing date of the parent Lal '080 application, it was well-established in the art that:

polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;

with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;

expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;

each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and

failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function, or the biological function of the polypeptide it encodes. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Rockett Declaration, the Iyer Declaration, and the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise biological function.

I. The applicable legal standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is “practically useful,” *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a “specific benefit” on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

An invention is “useful” under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) (“to violate Section 101 the claimed device must be totally incapable of achieving a useful result”); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention “is incapable of serving any beneficial end”).

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: “[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility.” *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a “nebulous expression” such as “biological activity” or “biological properties” that does not convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be “substantial.” *Brenner*, 383 U.S. at 534. A “substantial” utility is a practical, “real-world” utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a “well-established” utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examining Procedure at § 706.03(a). Only if there is no “well-established” utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The

applicant need only prove a “substantial likelihood” of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Use of the claimed polynucleotides in disease diagnosis and treatment and in drug discovery and toxicology testing are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are “well-established” uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application’s specification. These uses are explained, in detail, in the Rockett Declaration, Iyer Declaration, and Bedilion Declaration accompanying this brief. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of the claimed LABP-5 encoding polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer “specific benefits” to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Rockett Declaration, Iyer Declaration, and Bedilion Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

This United States patent application is the National Stage of International Application No. PCT/US00/05133, filed February 29, 2000, which claims the benefit under 35 U.S.C. § 119(e) of provisional application U.S. Ser. No. 60/122,080, filed March 1, 1999 (hereinafter the Lal ‘080 application).

In his Declaration, Dr. Rockett explains the many reasons why a person skilled in the art in 1999 would have understood that any expressed polynucleotide is useful for a number of gene expression monitoring applications, *e.g.*, in cDNA microarrays, in connection with the

development of drugs and the monitoring of the activity of such drugs. (Rockett Declaration at, e.g., ¶¶ 10-18).

It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s . . . that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology.¹ [Rockett Declaration, ¶ 18.]

In his Declaration, Dr. Bedilion explains why a person of skill in the art in 1999 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. (Bedilion Declaration, e.g., ¶¶ 4-7.) In his Declaration, Dr. Iyer explains why a person of skill in the art in 1999 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that “[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe.” (Iyer Declaration, ¶ 9.)]

In addition, Dr. Rockett explains in his Declaration that “there are a number of other differential expression analysis technologies that precede the development of microarrays, some by decades, and that have been applied to drug metabolism and toxicology research, including: (1) differential screening; (2) subtractive hybridization, including variants such as chemical cross-linking subtraction, suppression-PCR subtractive hybridization and representational difference analysis; (3) differential display; (4) restriction endonuclease facilitated analyses, including serial analysis of gene expression (SAGE) and gene expression fingerprinting and (5) EST analysis.” (Rockett Declaration, ¶ 7.)

Nowhere does the Patent Examiner address the fact that, as described on pages 41-42 of the Lal ‘080 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of

"Use of the words ‘it is my opinion’ to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon v. Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

Literature reviews published shortly after the filing of the Lal '080 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.

* * *

Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.

* * *

Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities

between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis in original)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, Xenobiotica 29:655-691 (July 1999) (Rockett Declaration, Exhibit C).

In a pre-March 1, 1999 article, Lashkari et al. state explicitly that sequences that are merely “predicted” to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay. (emphasis added)

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proc. Nat. Acad. Sci. 94:8945-8947 (Aug. 1997) (Reference No. 11).

B. The use of polynucleotides coding for polypeptides expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now “well-established”

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, e.g., as described by Bedilion, Rockett, and Iyer in their Declarations.

Toxicology testing is now standard practice in the pharmaceutical industry. See, e.g., John C. Rockett et al., *supra*:

Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett Declaration, Exhibit C, page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 14); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 15).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA arrays to toxicology, Environ. Health Perspec. 107:681-685 (1999) (Reference No. 16). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 17), indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene

which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 5) and published PCT applications WO 95/21944 (Reference No. 1), WO 95/20681 (Reference No. 2), and WO 97/13877 (Reference No. 7).

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function. . . . [abstract]

The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]

The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof." [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . [or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 - 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]

It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a

'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]

Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]

Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Appellants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression *patterns*, or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

The invention provides a "method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens." [abstract]

"[W]e see each individual gene product as a 'pixel' of information which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood." [page 2]

"The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts." [page 6]

"High resolution analysis of gene expression be used directly as a diagnostic profile. . . ." [page 7]

"The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed." [page 7]

"The invention . . . includes a method of comparing specimens containing gene transcripts." [page 7]

"The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens." [i.e., the results yield analogous data to microarrays] [page 8]

"Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made." [page 8]

"In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities." [page 9]

"In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . ." [page 9]

"[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells." [pages 9 - 10]

"The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as 'gene transcript image analysis' or 'gene transcript frequency analysis'. The present invention allows one

to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism." [page 11]

"The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few." [page 12]

"[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates." [page 12]

"For example, gene transcript frequency analysis can be used to differentiate normal cells or tissues from diseased cells or tissues. . . ." [page 12]

"In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . ." [page 12]

"In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond." [page 12]

"In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models." [page 14]

"In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition." [page 14]

"An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined." [page 15]

"[T]his research tool provides a way to get new drugs to the public faster and more economically." [page 36]

"In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker." [page 38]

"[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients." [page 39]

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 1995, describes an expression profiling platform, the "genome reporter matrix", which is different from nucleic acid microarrays. Additionally describing use of nucleic acid microarrays, the '588 patent makes clear that the utility of comparing multidimensional expression datasets is independent of the methods by which such profiles are obtained. The '588 patent speaks clearly to the usefulness of such expression analyses in drug development and toxicology, particularly pointing out that a gene's failure to change in expression level is a useful result. Thus, with emphasis added,

The invention provides "[m]ethods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to obtain a drug response profile which provides a model of the transcriptional responsiveness of said organism to the candidate drug." [abstract]

"The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising substantially all targets in a pathway [or] organism." [col. 1]

"The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. Suitable ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes. We term such a substantially comprehensive ensemble a genome reporter matrix." [col. 2]

"Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50

other reports, the first compound is, a priori, more likely to have fewer side effects." [cols. 2 - 3]

"Furthermore, it is not necessary to know the identity of any of the responding genes." [col. 3]

"[A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical." [col. 4]

"The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters." [col. 4]

" A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included." [cols. 6 - 7]

"In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form reference response profiles that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . The drug induces a complex response pattern of repression, silence and induction across the matrix The response profile reflects the cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug." [cols. 7 - 8]

"In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . [and] then

contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, under conditions where each of the transcripts hybridizes with a corresponding one of the probes to form hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile." [col. 8]

"The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses." [col. 8]

"Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli." [col. 9]

"The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s)." [col. 9]

The August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (reference "8" attached hereto), and the September 15, 1997 news report by Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," *Genetic Engineering News* (reference "9" attached hereto), attest the commercial value of the methods and technology described and claimed in the '588 patent.

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), published April 17, 1997, describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the reference describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

"[T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates." [Field of the invention]

"An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems." [page 3]

"Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals." [page 3]

"The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity." [page 3]

"As used herein, the terms 'gene expression profile,' and 'gene expression pattern' which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . . . Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand." [page 7]

"The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . ." [page 7]

Therefore, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Evidence of the benefits of this information include:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.
- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.
- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar

experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the “well-established” utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner’s rejections should be overturned regardless of their merit.

C. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility demonstrates utility

In addition to having substantial, specific and credible utilities in numerous gene expression

monitoring applications, the utility of the claimed polynucleotide can be imputed based on the relationship between the polypeptide it encodes, LABP-5, and another polypeptide of unquestioned utility, a mouse haemopoietic membrane protein, JB542 (see Baird et al., supra).

The two polypeptides have sufficient similarities in their sequences that a person of ordinary skill in the art would recognize more than a reasonable probability that the polypeptide encoded for by the claimed invention has utility similar to JB542. Appellants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed, and readily apparent from the patent application, that the polypeptide encoded for by the claimed polynucleotide shares more than 77% sequence identity over 132 amino acid residues with JB542. See specification, at Table 2. It further noteworthy that the two proteins share two transmembrane domains identified in JB542 from approximately amino acid residues 40 to 60 and at amino acid residues 90-110 of JB542. See Baird et al., at page 9192 and the attached sequence alignment, Exhibit A. This is more than enough homology to demonstrate a reasonable probability that the utility of JB542 can be imputed to the claimed invention (through the polypeptide it encodes). It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., Proc. Natl. Acad. Sci. 95:6073-78 (1998) (Reference No. 12). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the polypeptide encoded for by the claimed polynucleotide is related to JB542 is, accordingly, very high.

The Examiner must accept the Appellants' demonstration that the homology between the polypeptide encoded for by the claimed invention and JB542 demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

The Examiner has stated that the specification has not shown that LABP-5 has primary structural similarity with the polypeptide encoded by Baird et al. See Office Action, at page 5. However, the specification discloses at Table 2 that LABP-5 was identified as homologous to JB542 (g3355655) using BLAST analysis, and further discloses BLAST analysis as sequence alignment tool in Table 5 of the specification. It is therefore a routine matter in the art to obtain a BLAST alignment of the two proteins as presented in Exhibit A to obtain the information disclosed above.

D. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies

who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. Page et al., in discussing the identification and assignment of candidate drug targets, state that "rapid identification and assignment of candidate targets and markers represents a huge challenge ... [t]he process of annotation is similarly aided by the quantity and richness of the sequence specific databases that are currently available, both in the public domain and in the private sector (e.g. those supplied by Incyte Pharmaceuticals)" Page, M.J. et al., "Proteomics: a major new technology for the drug discovery process," *Drug Discov. Today* 4:55-62 (1999) (Reference No. 18), see page 58, col. 2). As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's invention of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase the claimed polynucleotide directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described *supra*.

III. The Patent Examiner's rejections are without merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific, substantial, and credible" utilities. (Office Action at page 4). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The precise biological role or function of an expressed polynucleotide is not required to demonstrate utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention

either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the First Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

[T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Because the uses of LABP-5 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility

The PTO rejected the claims at issue on the ground that the use of an invention as a tool for research is not a “substantial” use. See Office Action, top of page 8. Because the PTO’s rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section § 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools):

Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact “useful” in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The Patent Office’s actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO’s Training Materials themselves to be useful, as well as DNA sequences used, for example, as markers.

Only a limited subset of research uses are not “substantial” utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 (“What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.”).

Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

C. The Patent Examiner failed to demonstrate that a person of ordinary skill in the art would reasonably doubt the utility of the claimed invention

The Examiner dismissed any utility for the polypeptide encoded by the claimed polynucleotide based on sequence homology with the Baird protein, JB542, stating that LABP-5 “has not been shown to have primary structural similarity with polypeptides present in Baird et al ...”, and further that “even if they did demonstrate a level of structural homology, since the function of LABP is not known it would not be conclusive to assume, solely based on structure homology, that they have the same function and would have the same utility.

Applicants have previously addressed the fact that sufficient information is disclosed in Tables 4 and 5 for the skilled artisan to ascertain the specific sequence alignment and sequence homology between LABP-5 and JB542 using BLAST analysis as demonstrated in Exhibit A. Baird et al. disclose that the expression of JB542 specifically in undifferentiated haemopoietic stem cells coupled with the characterization of the protein as a transmembrane protein (a property shared by JB542) is sufficient to propose its potential use as a cell differentiation marker. Such a utility is entirely independent of the biological function of the protein or its encoding polynucleotide for reasons discussed supra. Likewise, for reasons discussed above (see § II.C), with a 77% sequence identity between LABP-5 and JB542 coupled with retention of the two transmembrane domains, the skilled artisan would readily recognize the substantial likelihood that LABP-5 would similarly be useful as a cell surface marker for cell differentiation.

Applicants’ Showing of Facts Overcomes The Examiner’s Concern That Applicants’ Invention Lacks “Specific Utility”

The Examiner alleges that applicants assertions of utility are not specific, but “are general and would apply to any polynucleotide” (Office Action, page 6.)

Appellants’ submission of additional facts overcomes this concern. Those facts demonstrate that, far from applying *regardless* of the specific properties of the claimed

invention, the utility of Appellants' claimed polynucleotides as gene-specific probes *depends upon* specific properties of the polynucleotides, that is, their nucleic acid sequences.

"[E]ach probe on . . . [a "high density spotted microarray[]"], with careful design and sufficient length, and with sufficiently stringent hybridization and wash conditions, *binds specifically* and with minimal cross-hybridization, to the probe's cognate transcript"¹; "[e]ach gene included as a probe on a microarray provides *a signal that is specific to the cognate transcript*, at least to a first approximation."² Accordingly, "each additional probe makes an additional transcript newly detectable by the microarray, increasing the detection range, and thus versatility, of this analytical device for gene expression profiling"³; equally, "[e]ach new gene-specific probe added to a microarray thus increases the number of genes detectable by the device, increasing the resolving power of the device."⁴

Although not required for present purposes, it would be appropriate to state on the record here that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established underpinning of many, perhaps most, molecular biological techniques developed over the past 30 - 40 years.

IV. By requiring the patent applicant to assert a particular or unique utility, the Patent Examination Utility Guidelines and Training Materials applied by the Patent Examiner misstate the law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

¹ Declaration of Dr. John C. Rockett, ¶ 10(i), emphasis added.

² Declaration of Dr. Vishwanath R. Iyer, ¶ 7 (emphasis added). See the footnote at ¶ 7 for a slightly more "nuanced" view.

³ Declaration of Dr. John C. Rockett, ¶ 10(ii).

⁴ Declaration of Dr. Vishwanath R. Iyer, ¶ 7.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities:

“specific” utilities which meet the statutory requirements, and “general” utilities which do not.

The Training Materials define a “specific utility” as follows:

A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as “gene probe” or “chromosome marker” would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between “specific” and “general” utilities by assessing whether the asserted utility is sufficiently “particular,” *i.e.*, unique (Training Materials at page 52) as compared to the “broad class of invention.” (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) (“With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.”)).

Such “unique” or “particular” utilities never have been required by the law. To meet the utility requirement, the invention need only be “practically useful,” *Natta*, 480 F.2d 1 at 1397, and confer a “specific benefit” on the public. *Brenner*, 383 U.S. at 534. Thus, incredible “throw-away” utilities, such as trying to “patent a transgenic mouse by saying it makes great snake food,” do not meet this standard. Karen Hall, Genomic Warfare, *The American Lawyer* 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where “specific utility” is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be “definite,” not particular. *Montedison*, 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not “particular” or “unique” to the specific invention. Where courts have found utility to be too “general,” it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a

specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had “useful biological activity” was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a “particular” type of cancer was determined to satisfy the specificity requirement). “Particularity” is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. (*Montedison*, 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of “general” utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. See *supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

CONCLUSION

Appellants therefore request that the rejections of claims 3-6, 10 and 11 under 35 U.S.C. § 101 be reversed for at least the above reasons.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 3-7, 9, 11 and 48 (Enablement)

The Examiner has rejected claims 3-6, 10 and 11 under 35 U.S.C. § 112, first paragraph, specifically, since the claimed invention is not supported by either a specific and substantial

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants Response

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under 35 U.S.C. § 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 U.S.C. § 101, it fails for the same reasons. Withdrawal of the rejection of claims 3-6, 10 and 11 under 35 U.S.C. § 112, first paragraph, is therefore requested.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 3-6, 10 and 11 (Written Description)

The Examiner has rejected claims 3-6, 10 and 11 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated that the claims as presented encompass genomic DNA. The LABP-5 protein clone was obtained from a cDNA library. The structure and sequence of the chromosomal DNA is not disclosed in sufficient detail, so that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention. The person skilled in the art would not recognize in the current disclosure a description of the invention defined by the claim as it relates to genomic DNA for several reasons. There are no examples of genomic DNA disclosed. The coding sequences disclosed do not contain any introns sequences(s) since the sequences are cDNA, which is made of only exon sequences. For these reasons, it does not appear that applicants were in possession of the claimed invention as it pertains to genomic DNA at the time the application was filed.

Applicants Response

Applicants strongly disagree that the claimed polynucleotides encoding LABP-5 encompass genomic sequence. As the Examiner has acknowledged, a “cDNA” is composed entirely of extronic sequences because it is the “complementary” DNA of transcribed messenger RNA in which all intronic sequences of the genomic DNA have been removed. The claimed

“isolated polynucleotide encoding a polypeptide of SEQ ID NO:5” as recited in claim 3, encompasses only the coding sequence for SEQ ID NO:5, as found, for example, in SEQ ID NO:10. It cannot therefore encompass the genomic DNA sequence which applicant does not claim to be in possession of. With respect to potential splice variants arising from alternative exon splicing as the Examiner has alluded to, again, no claim to such splice variants, or any other variants for that matter are recited in the claim. Withdrawal of the rejection of claims 3-6, 10 and 11 under 35 U.S.C. § 112, first paragraph for lack of adequate written description is requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited. Applicants further request that upon allowance of claims 3-6, 10 and 11, claims 8, 12-14 23 and 27 be rejoined and examined as process claims that depend from and are of the same scope as allowable product claims in accordance with *In re Ochiai* and the MPEP § 821.04.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

Respectfully submitted,

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Date: April 30, 2004

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Attachment(s):

Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with attached Exhibits A-Q

Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E

Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132

Exhibit A: Sequence Alignment, LABP-5 vs JB542 by BLAST analysis

Sixteen (16) references:

1. PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995)
2. PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995)
3. M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995)
4. PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995)
5. U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996)
6. R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997)
7. PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997)
8. Acacia Biosciences Press Release (August 11, 1997)
9. V. Glaser, Strategies for Target Validation Streamline Evaluation of Leads, Genetic Engineering News (September 15, 1997)
10. J. L. DeRisi et al., Exploring the metabolic and genetic control of gene expression on a genomic scale, Science 278:680 - 686 (October 24, 1997)
11. S. E. Brenner et al., Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998)
12. J. C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (1999)
13. E. F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999)
14. S. Steiner and N. L. Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000)
15. Email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding
16. M. J. Page et al., Proteomics: a major new technology for the drug discovery process, Drug Discov. Today 4:55-62 (1999)